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Inventors: Lam, Eric  
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#### **REMARKS**

Claims 1-32 are pending in the instant application. Claims 1-32 have been rejected. Claim 1 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

#### **I. Withdrawn Objections**

Applicant acknowledges withdrawal of objections to the specification and claims.

#### **II. Rejection of Claims Under 35 U.S.C. §112**

Claims 1-32 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, claim 1 has been rejected because for reciting "heterologous DNA segments". It is suggested that the specification does not discuss constructs that contain multiple heterologous DNA segments. Thus, claim 1 has been amended to recite "a heterologous DNA segment". In light of this amendment, it is respectfully requested that the rejection of claims 1-32 under 35 U.S.C. §112, second paragraph, be withdrawn.

The rejection of claims 24-32 under 35 U.S.C. §112, first paragraph, has been maintained. It is suggested that while the specification is enabling for a DNA construct for integration of a heterologous DNA segment into genomes, wherein the DNA construct is adapted for integrating a heterologous DNA segment at a pre-determined location in the Chlamydomonas genome, and a method for inserting a heterologous DNA molecule into a pre-

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determined location of a Chlamydomonas genome, does not reasonably provide enablement for DNA constructs adapted for integrating a heterologous DNA segment into pre-determined locations of other plant genomes, or methods for inserting a heterologous DNA into a pre-determined location in other plant genomes, or a method of activation tagging of a plant genome. Applicant respectfully traverses this rejection.

In accordance with MPEP 2164.01, the test of enablement is based on whether the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Factors to be considered include:

(A) *The breadth of the claims*

The rejected claims encompass inserting a heterologous DNA molecule into a pre-determined location on any plant genome.

(B) *The nature of the invention*

The invention is the use of an improved, well-defined construct to minimize the number of independent transformation events required to obtain the infrequent homologous recombination events and streamline the recovery of low-frequency homologous recombination events by suppressing or eliminating complex integration processes. See page 5, lines 14-33, of the instant specification.

(C) *The state of the prior art*

In response to Applicant's arguments filed December 9, 2004, the Examiner suggests that because Puchta ((2001) *Plant Mol. Biol.* 48:173-182) teaches frequency of gene targeting in plants is low enough that gene targeting is not feasible, this indicates that techniques for homologous recombination were not known in

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the art (page 4, first paragraph). Applicant respectfully disagrees with this interpretation. Puchta specifically teaches that gene targeting in plants such as *Arabidopsis* and *Physcomitrella* had been achieved at the time of filing, albeit efficient gene targeting techniques had not been fully developed. See abstract and paragraph bridging pages 174 and 175 of Puchta. Thus, the necessary techniques for preparing constructs, transforming plant cells, and screening for gene targeting events were well-known in the art at the time of filing.

(D) *The level of one of ordinary skill*

The level of one of ordinary skill in the art was quite high at the time of filing as evidenced by the teachings of Miao and Lam ((1995) *Plant J.* 7:359-365). This reference teaches construction of a gene targeting vector (Figure 1 and page 363, column 2, last full paragraph); transformation of plant cells (page 364, column 1, first full paragraph); and screening and identification of homologous recombinants (page 364, column 1, paragraphs 2 and 3). Accordingly, the skilled artisan would have all the necessary tools available for practicing the methods of the instant invention.

(E) *The level of predictability in the art*

At the time of filing there was predictability in the art for obtaining a homologous integrant. Puchta teaches that independent of plant species (tobacco or *Arabidopsis*), a gene targeting event could be obtained at a frequency of 1 out of every 10,000 to 100,000 random integration events (see page 174, line bridging column 1 and 2). Thus, while the number of transformants to be screened was high, this type of screening was routine and predictable in the art.

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(F) *The amount of direction provided by the inventor*

There is considerable guidance provided by the specification as to how to carry out the integration of a heterologous DNA segment at a pre-determined location on a plant genome using a construct of the instant invention. For example, Figure 1 and pages 17-20 disclose the necessary elements of a gene targeting construct of the instant invention; pages 20-21 teach methods for transforming plants; and Figure 2 and pages 25-26 teach how to select and screen for the desired homologous integrants.

(G) *The existence of working examples*

MPEP 2164.02 states that an example may be "working" or "prophetic." In accordance with this requirement, the specification provides a clear prophetic example at pages 22-26 which teaches transposon-based gene targeting for plants using *Agrobacterium* vectors.

(H) *The quantity of experimentation needed to make or use the invention based on the content of the disclosure.*

The specification as a whole, the Figures, and Example 1 beginning at page 22 provides considerable direction and guidance to one of skill in the art as to the selectable markers, transposons, and screening protocol to produce and identify the desired homologous integrants. Therefore, the amount of experimentation necessary to carry out the steps of the invention would not be undue. Further, the basis of the instant invention is to improve upon existing techniques having frequencies of  $10^{-4}$  to  $10^{-5}$  to minimize the number of independent transformation events required to obtain the infrequent homologous recombination events and streamline the recovery of low-frequency homologous recombination events by suppressing or eliminating complex

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integration processes. Therefore, by incorporating the novel features of the instant construct and methods into the routine practices carried out by one of ordinary skill, the artisan could generate plants with homologous recombination events without an undue amount of experimentation and use said plants in accord with known utilities, e.g., those disclosed in the instant specification at page 5, lines 4-8.

Thus, Applicant has met the enabling requirement of the first paragraph of Section 112 by providing a disclosure that informs those skilled in the relevant art how to both make and use the claimed invention. Further, it is improper to require evidence of the degree of effectiveness (MPEP 2107.02) by demonstrating a homologous recombination event in a plant, when the art has established that homologous recombination occurs in plants and the instant invention is an improvement upon the existing technology. Accordingly, it is respectfully requested that this rejection be reconsidered and withdrawn.

### **III. Rejection of Claims Under 35 U.S.C. §103**

Claims 1-23 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Yoder et al. (WO 92/01370) in view of Hashimoto et al. ((1999) *Plant Sci.* 141:175-181), Bayley et al. ((1992) *Plant Mol. Biol.* 18:353-361) and Suter Crazzolara et al. ((1995) *Meth. Cell. Biol.* 50:425-438). The Examiner suggests the Yoder et al. teach methods to introduce heterologous DNA into genomes using transposon systems comprising substrate sites recognized by a transposase, selection and marker genes, and heterologous genes of interest wherein the transposon system can be introduced into plants by any means including *Agrobacterium* in

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which the transposon system is within the borders of the *Agrobacterium* tDNA. The Examiner acknowledges that Yoder et al. do not teach the cytosine deaminase (coda) gene.

It is suggested that Hashimoto et al. teach the use of cytosine deaminase as a negative selection marker in plant systems.

The Examiner suggests that Bayley et al. teach the use of the Cre-lox recombination system to excise a luciferase gene from the genome of a tobacco plant, wherein the use of the this strategy yields cells devoid of DNA markers that are not longer required.

It is suggested that Suter-Crazzolara et al. teach several detectable marker genes, including GUS.

The Examiner suggests that it would have been obvious at the time of filing to modify the method of Yoder et al. by using any other selection marker gene, such as the cytosine deaminase gene as taught by Hashimoto et al, as Hashimoto asserts that this gene is good for use in plant systems. It is suggested that it would have been obvious to place the cloning sites anywhere outside of the transposase substrate sites in the construct of Yoder et al., including the termini of the construct, to facilitate introduction of the genes of interest. It is further suggested that it would have been obvious to place polylinker sites within the transposase substrate sites, to facilitate insertion of further selection, marker or other heterologous genes. The Examiner also suggests that it would have been obvious to modify the DNA construct by inserting a detectable marker gene within the construct such that a transposase substrate site was in between the promoter and marker coding sequence, following the

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strategy used by Bayley et al. given that Bayley et al. demonstrate this strategy provides another tool to monitor the excision event following the action of the transposase, and their assertion that the excision event yields cells devoid of unwanted DNA markers. It is further suggested that it would have been obvious to use any detectable marker gene other than luciferase, such as those taught by Suter-Crazzolara et al. Applicant respectfully traverses this rejection.

MPEP 2143.01 indicates that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Further, the courts have held that although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." [emphasis added] 916 F.2d at 682, 16 USPQ2d at 1432.).

Yoder et al. teach at page 10, lines 5-14, that a vector of the disclosure "typically contains an ancillary selectable marker gene by which transformed plant cells can be identified in culture. Usually, the marker gene will encode antibiotic resistance." From this passage and the remaining disclosure, it is clear that Yoder et al. do not contemplate the use two selectable markers. Further, the markers disclosed by Yoder et al. are routinely used for positive selection, i.e., G418, hygromycin, bleomycin, kanamycin, methotrexate, chlorsulfuron, lincomycin, clindamycin, spectinomycin, phosphinotricine, glyphosate and gentamicin. Accordingly, while the vector of Yoder et al. could be modified to function the way the DNA construct of

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the instant invention is claimed, there is simply is no suggestion or motivation in Yoder et al. to employ two selectable markers, one positive and one negative, in a DNA construct for integration of heterologous segments into genomes within cells. Likewise, the teachings of Hashimoto et al., Bayley et al. and Suter-Crazzolara et al. fail to teach or suggest positive and negative selection in a DNA construct. As such the cited references fail to establish a *prima facie* case of obviousness because these references fail to teach or suggest all the limitations of the instant claims. See MPEP 2143.03. It is therefore respectfully requested that this rejection be withdrawn.

Claims 29-32 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over Yoder et al. in view of Hashimoto et al., Bayley et al., and Suter-Crazzolara et al. as applied to claims 1-23 above, and further in view of Walden et al. ((1994) *Plant Mol. Biol.* 26:1521-28). It is suggested that Yoder et al., Hashimoto et al., Bayley et al., and Suter-Crazzolara et al. teach DNA constructs for integration of DNA segments into cell genomes, as discussed above. The Examiner suggests that Walden et al. teach a method for activation tagging of plant genomes, using a vector comprising promoter enhancer sequences to activate expression of genes in genomes, thereby producing mutants. It is suggested that it would have been obvious to further modify the DNA constructs taught by Yoder et al. in view of Hashimoto et al., Bayley et al., and Suter-Crazzolara et al. by inserting promoter enhancer sequences taught by Walden et al., thereby enabling the use of the DNA construct in activation tagging of plant genomes. Applicant respectfully traverses this rejection.



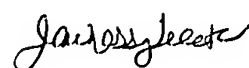
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In so far as claims 29-32 are dependent on claim 1, these claims are not obvious in view of Yoder et al., Hashimoto et al., Bayley et al., Suter-Crazzolara et al. and Walden et al. for the reasons stated above. Thus, when an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP §2143.03. Thus, withdrawal of the rejection of claims 29-32 is respectfully requested.

#### IV. Conclusion

The Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



Jane Massey Licata  
Registration No. 32,257

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Licata & Tyrrell P.C.  
66 E. Main Street  
Marlton, New Jersey 08053

(856) 810-1515